REMARKS

Claims 2-5 have been cancelled without prejudice; claim 10 has been amended; and new claims 11-13 have been added. Support for the new claims is found throughout the specification as well as the original claim 5. Therefore, claims 1 and 10-13 are pending in the application.

In the specification, Example 6 was deleted from page 17, renumbered as Example 10, and reinserted at the end of all the Examples of the specification on page 22. The Examples were renumbered and rearranged to follow each other in a more logical manner. Moreover, the title of this Example was corrected from "Preparation of insulin from mono-Arg insulin" to "Preparation of insulin from mini-proinsulin." This was an obvious error apparent from the context of the specification. Therefore, no new matter has been added. The same mistake in the first line of this Example was corrected similarly.

In the Office Action mailed January 21, 1992, the Examiner rejected claim 5 under 35 U.S.C. § 101 asserting that it "is drawn to a use of a compound which is a non-statutory invention." Claim 5 has been cancelled and rewritten as new claim 11. It now recites a method for the preparation of the compound of formula II ... using the compound of formula I, as claimed in claim 1. The amendment has overcome the 35 U.S.C. § 101 rejection, therefore, the withdrawal of this rejection is respectfully requested.

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The Examiner rejected claims 2-4 under 35 U.S.C. § 101. Applicants have cancelled claims 2-4 without prejudice or disclaimer of the subject matter thereof. Therefore, this rejection is moot and its withdrawal is respectfully requested.

Claims 1-5 were rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Markussen et al. (EPO 163,529), and §102(e) as being anticipated by Markussen et al. (USSN 4,946,828). The Examiner asserted that

> Both Markussen et al. references disclose the insulin variant B(1-29)-Arg-A(1-21) of human insulin produced recombinantly in yeast. As such, this precursor protein before cleavage and the method of producing the cleaved human insulin variant are inherently disclosed. (See column 15; Table 1, column 17, and claims in '828.) This information has been incorporated into the patent from EPO 163,529. (See column 14, lines 42-43.) Both references further teach use of the insulin variants as pharmaceuticals.

Applicants respectfully traverse these rejections.

For a reference to anticipate the claimed invention under 35 U.S.C. § 102, it is axiomatic that it discloses and enables all the elements of the claimed invention. Neither one of the Markussen references, however, include every element of the claimed invention.

EP-A 0,163,529 relates to insulin precursors wherein the B chain is shortened, B(1-29), and the C chain is either missing completely or is shortened to one amino acid. These precursors are then converted into mature human insulin by

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trypsin-catalyzed transpeptidation using an α-threonine ester.

In contrast with EP-A 0,163,529, the claimed invention relates to human Des-(32-65) proinsulin or mini-proinsulin wherein B(1-30) and A(1-21) chains of human insulin are connected via arginine. This compound is used not only as an intermediate for the preparation of human insulin and "mono-Arg-insulin" but also shows a certain insulin activity itself.

EP-A 0,163,529 does not disclose the claimed invention wherein the B chain is composed of 30 amino acids and the C chain is replaced with a single arginine residue. The formula B(1-29)-$(X_n-Y)_m$-A(1-21), as described on page 5 of EP-A 0,163,529, is a generic one encompassing a vast number of compounds. However, the disclosure of EP-A 0,163,529 does not specifically enable the claimed compound of the formula B(1-30)-Arg-A(1-21). Without an enabling disclosure and in light of the unpredictability of the chemical arts, the cited reference does not describe and cannot anticipate the claimed invention. Applicants point out that the preferred compounds, described in the EP-A 0,163,529, are different from the claimed invention of the present application.

The cited U.S. Patent No. 4,946,828 does not disclose the claimed compound of the formula B(1-30)-Arg-A(1-21), either. In fact, all compounds described in this cited reference differ from the claimed mini-proinsulin of the present application. Furthermore, the reference of the European

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patent application 0,163,529, in column 14, lines 42-43 of this U.S. patent, relates to the specific DNA fragments encoding the claimed insulin analogs which are different from the claimed invention. Therefore, the cited Markussen U.S. patent does not anticipate the claimed proinsulin.

In light of the foregoing remarks, applicants respectfully request that the rejections under 35 U.S.C. § 102(b) and (e) be withdrawn.

The Examiner rejected claim 10 under 35 U.S.C. § 103 as being unpatentable over Markussen et al. (EPO 163,529) or Markussen et al. (U.S. Patent No. 4,496,828) in view of Goeddel et al. (EP-A 0,055,945), for the reasons asserted on pages 4-5 of the Office Action. Applicants respectfully traverse this rejection.

As pointed out above, in response to the § 102 rejections of claims 1-5, the cited Markussen references do not disclose the specific claimed proinsulin of the present invention comprising the formula B(1-30)-Arg-A(1-21). Moreover, because of the unpredictability of the chemical arts and in the absence of an enabling disclosure, one of ordinary skill in the art would not have known how to make and use the claimed compound. The secondary reference of Goeddel et al. does not provide any more information to cure the deficiencies of the two primary references. The amended claim 10 now depends on claim 1 and therefore, includes all the limitations of claim 1. As described above, the cited references,

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singly or in combination, do not teach or suggest the invention of claim 1, much less could they be sufficient for establishing a prima facie case of obviousness for the invention of claim 10 which is dependent on claim 1. Therefore, the applicants respectfully request the withdrawal of the 35 U.S.C. § 103 rejection.

The Examiner objected to the specification and rejected claims 1-5 and 10 under 35 U.S.C. § 112, first paragraph. The Examiner stated that the specification fails to provide an adequate written description and enabling disclosure. Applicants respectfully traverse this objection and rejection. The Examiner's specific arguments are addressed as follows.

The Examiner contended that the specification does not clearly describe what is intended by a "one-pot reaction"; and that it is unclear whether this limitation of claim 5 is enabled by the specification. Applicants respectfully point out that "one-pot reaction" is a well-known term of the art. One of ordinary skill in the art knows that in a "one-pot reaction", no intermediates have to be isolated. Rather, the end product may be directly isolated out of the reaction vessel in which the reaction process was started. Moreover, the paragraph bridging pages 4 and 5 of the specification clearly describes the meaning and scope of this term of art by way of comparison with the "two-pot reaction" needed to convert natural proinsulin to insulin. Furthermore, this limitation of the now cancelled claim 5, recaptured in new claim 13, is

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enabled throughout the specification, specifically in Example 10 (originally numbered as Example 6). In this example, all the reagents are added to mini-proinsulin in one vessel and insulin is isolated out of that same vessel by centrifugation.

The Examiner noted that "[t]he structure of formula II in claim 5 is not described nor its formation enabled by the specification." Claim 5 has been cancelled and rewritten as new claims 11-13. In new claim 11, the structure of the compound of formula II is identical to that of the mono-Arg insulin of the formula II on page 2 of the specification. The formation of this compound is enabled on page 2 of the specification where, in line 17, enzymatic cleavage is stated as a means for the preparation of this compound from the compound of formula I. Additionally, Example 10 (originally numbered as Example 6) describes in detail, a method of making this compound from the compound of formula I (mini-proinsulin).

The Examiner contended that the "ballast component", mentioned in claim 10, is not defined in the specification and that "it is unclear whether this limitation of claim 10 is enabled by the specification." Applicants assert that this term is commonly used by people of ordinary skill in the art. Moreover, the paragraph bridging pages 2-3 and Example 2 c) describe the fusion protein of claim 10 wherein the compound of the formula I is bonded via the bridging member -Met-Ile-Glu-Gly-Arg- to a "ballast component", here, the

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first 38 amino acids of the IL-2. One of ordinary skill in the art, reading claim 10 in light of the cited passages in the specification will be able to determine that the "ballast component" refers to the stabilizing component of the fusion protein. Solely in an effort to expedite the prosecution, however, claim 10 has been amended to replace "ballast component" with "a peptide which stabilizes."

The Examiner contended that the numbers in the specification, used to refer to different DNA fragments described in the Tables and Figures are confusing. Applicants point out that careful examination of the specification shows that the numerals within parentheses refer to DNA fragments. Each number within a parenthesis refers only to one and the same DNA fragment which may appear in the Tables as well as the Figures of the application. Other numerals which are not surrounded by parenthesis are referred to in the specification as oligonucleotides, e.g., oligonucleotide No. 4, also appear in the Tables as numerals not surrounded with parenthesis. These numerals mark different single stranded oligonucleotides shown in each Table. Applicants, in an effort to expedite the prosecution of this application, have amended the specification to specifically describe the numbering system. The amendment is merely a verbalization of what can be obviously deduced from the language of the specification and the consistent numbering of the DNA fragments and oligonucleotides. Th refore, no new matter has been introduced.

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In light of the amendments and the above remarks, applicants respectfully request the withdrawal of this objection and rejection under 35 U.S.C. § 112, first paragraph.

The Examiner rejected claims 2-5 and 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as the invention. Applicants respectfully traverse this rejection. Each of the Examiner's specific arguments are addressed as follows.

On page 5 of the Office Action, the Examiner contended that

> Claim 1 is indefinite for failing to clearly indicate that the compound of formula I is a single peptide chain with all amino acids contiguous. It is ambiguous to define 'B(1-30)' and 'A(1-21)' as the B and A chain of human insulin because these chains are known to be cleaved and attached to each other by disulfide bonds. As such, it is unclear what structure applicant is claiming, particularly how and where the additional arginine ('Arg') amino acid is connected to the structure.

Applicants respectfully point out that the description system used in claim 1 is one that is commonly used in the art, such as the Markussen patents cited by the Examiner. One of ordinary skill in the art, reading claim 1 in light of the specification will be able to understand that the compound of formula I is a single peptide chain with the B-chain covalently linked to the A-chain via an Arg residue and that it has the correct folding allowing its easy transformation into insulin which is described in the specification.

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The rejection of claims 2 and 3 are now moot since these claims have been cancelled by this amendment.

With regard to claim 10, the Examiner stated that it is duplicative of claim 1. The Examiner contended that claim 10 does not add further limitations to the compound of formula I. On page 7 of the Office Action, the Examiner noted that "while claim 10 is drawn to a fusion protein, no additional protein component is required to be fused to formula I. The phrase 'preferably bonded ... of the fusion protein' is functional language and given no patentable weight." On page 8 of the Office Action, the Examiner contended that the language of claim 10 "provides no indication of how or where (N-terminal or C-terminal) the bridging member is located or whether the bridging member, ballast component and compound of formula I are operably linked."

Applicants point out that the amended claim 10 now recites a fusion protein which comprises the mini-proinsulin of claim 1, bonded to a stabilizing peptide via a bridging member composed of -Met-Ile-Glu-Gly-Arg-. The Examiner is reminded that the claims must be viewed in light of the specification, which provides the method of making this fusion protein in the Examples. Claim 10 depends on claim 1, which is a mini-proinsulin, and limits claim 1 by the addition of the bridging component and the stabilizing peptide component to the mini-proinsulin. Moreover, it is intended that claim 10 encompasses both the C- and the N- terminal

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fusion proteins. Therefore, no particular distinction has been specified.

The rejection of claim 4 is now moot since this claim is cancelled without prejudice or disclaimer of the subject matter thereof.

The Examiner stated that in claim 5, it is unclear what the terms "arranged" and "one-pot reaction" encompass and what the phrase "or of insulin" is intended to mean. Moreover, the Examiner pointed out the typographical errors in the structure of formula II, i.e., the presence of two extra bonds connecting the sulfur atoms on lines 3 and 4 of this structure.

Claim 5 has been cancelled and its content has been recaptured in new claims 11-13. These new claims do not include "arranged" and "or of insulin." Although the term "one-pot reaction", as mentioned above, is a well-known term of the art and its meaning has been described in the paragraph bridging pages 4 and 5 of the specification by way of comparison to two-pot reaction, it has been amended to read "one vessel" in claim 13.

The Examiner rejected the language of claims 2-5 and 10 reciting the phrase "of the formula I". Applicants have cancelled claims 2-5. Claim 10 has been amended to properly depend on claim 1, per Examiner's suggestion.

In light of the amendments and the above remarks, applicants respectfully request the withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

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In view of the above amendment and remarks, Applicants submit that the claims pending in the subject patent application are in condition for allowance. A favorable action is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees (or credit any overpayment) associated with this communication to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. Section 1.136 not accounted for above, such extension is requested and should also be charged to our Deposit Account.

Respectfully submitted,

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By: Raz Fleshner
Raz E. Fleshner
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Date: April 21, 1992

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